

Diabetes Mellitus

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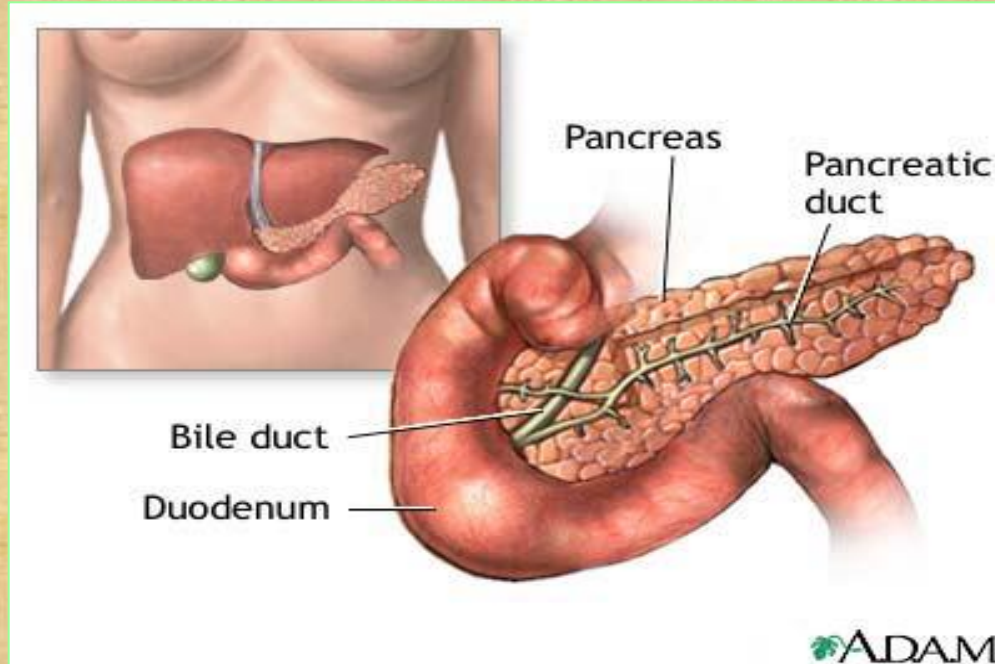
Ass. Prof. hematopathology

PNU

objective

- By the end of this session the student must be able to :
- Define Diabetes Mellitus
- Discriminate between different types of Diabetes.
- Histopathologic finding in diabetic patient complication

What is diabetes?



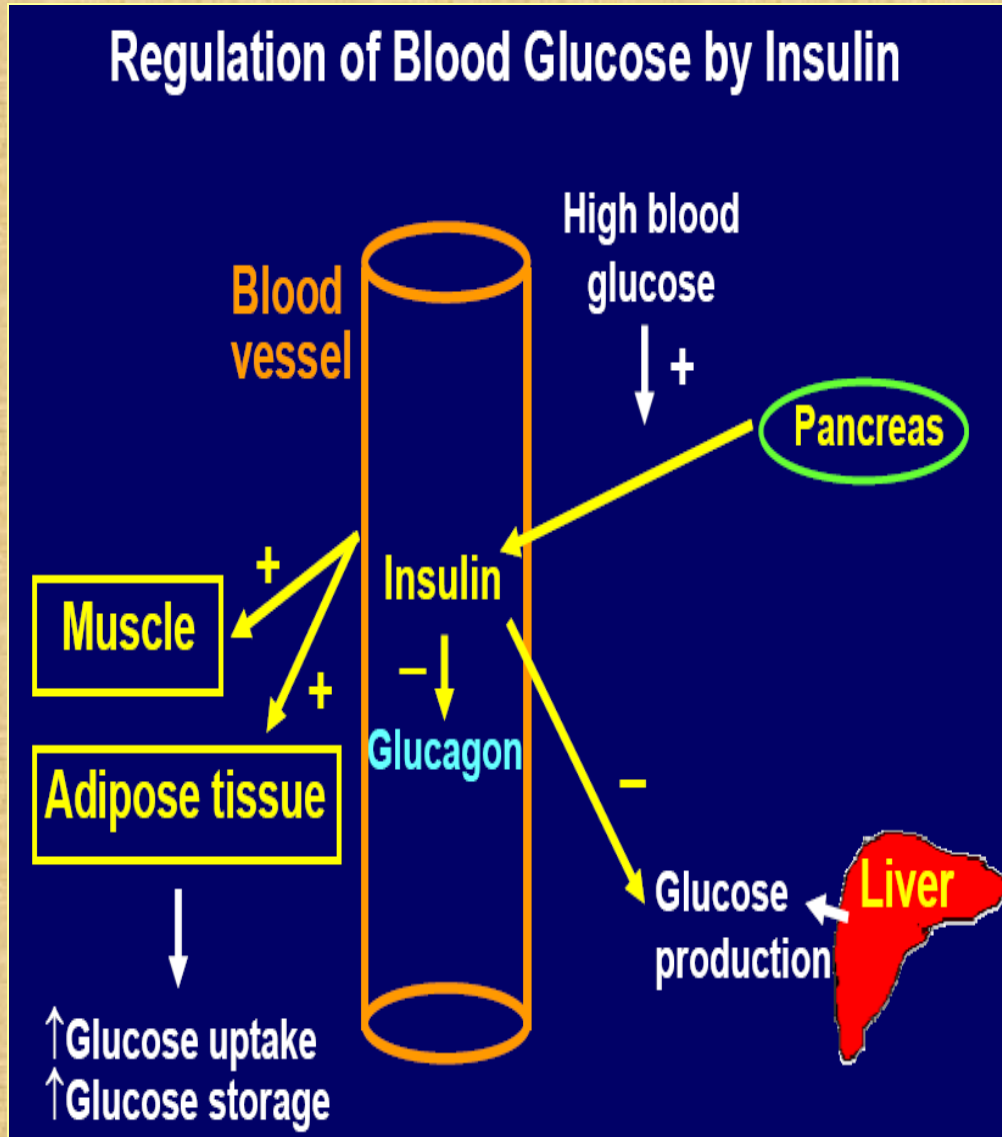
- **Diabetes mellitus (DM)** is a chronic condition that is characterised by raised blood glucose levels (**Hyperglycemia**).

Diabetes Mellitus

Definition

- A multisystem disease related to:
 - Abnormal insulin production, or
 - Impaired insulin utilization, or
 - Both of the above
- Leading cause of heart disease, stroke, adult blindness, and non-traumatic lower limb amputations

Regulation of Glucose homeostasis

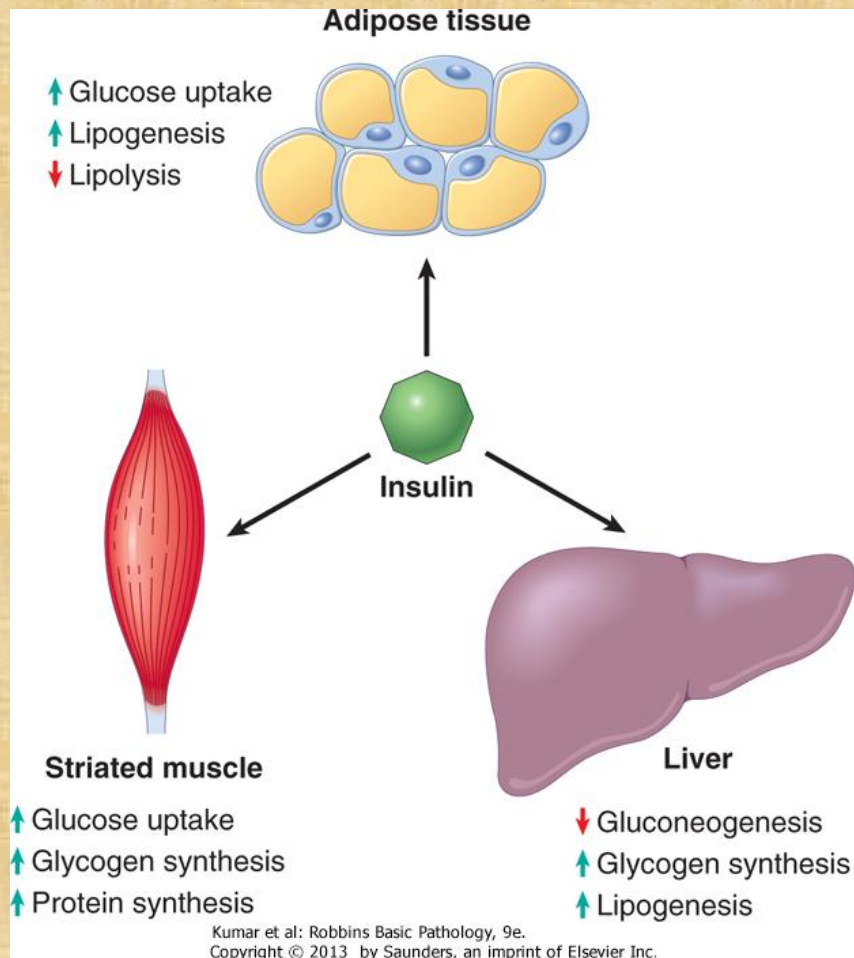


- (1) glucose production in the liver,
- (2) glucose uptake and utilization by peripheral tissues, chiefly skeletal muscle,
- (3) actions of insulin and counter regulatory hormones (e.g., glucagon).

Normal Insulin Metabolism

- Insulin Produced by the β cells in the islets of Langerhans of the pancreas
- Promotes glucose transport from the bloodstream across the cell membrane to the cytoplasm of the cell
- Analogous to a “key” that unlocks the cell door to allow glucose in

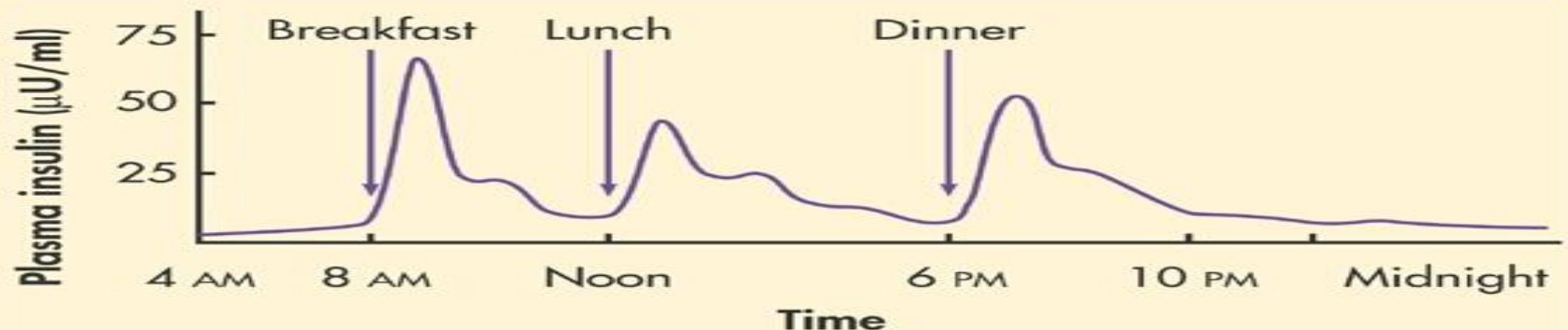
How Insulin decrease blood glucose level;



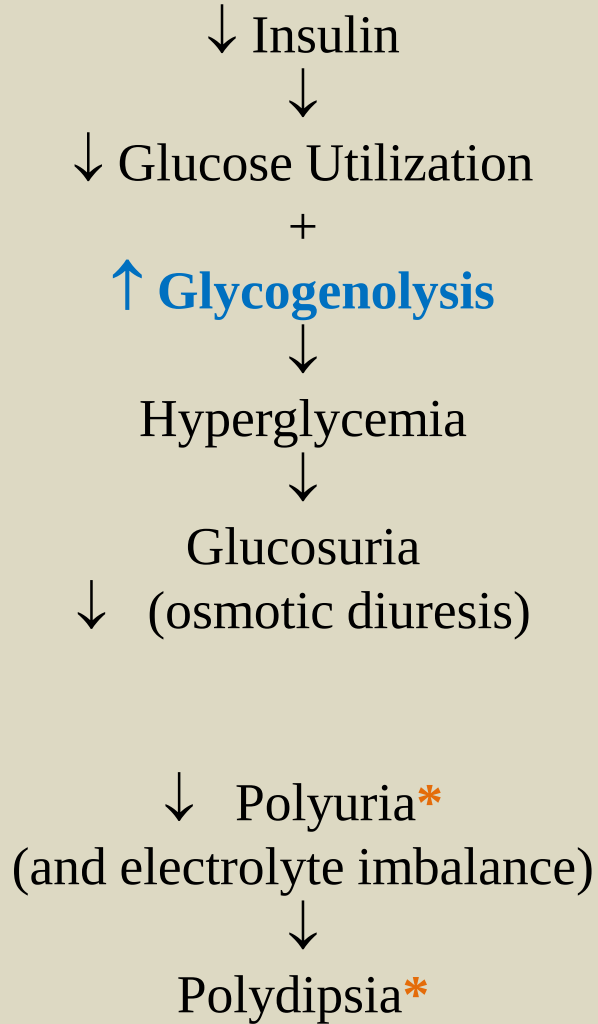
- the **metabolic effects** of insulin can be summarized as **anabolic**, with increased synthesis and reduced degradation of glycogen, lipid, and protein.
- Insulin **reduces the production of glucose from the liver.**
- The principal metabolic function of insulin is to **increase the rate of glucose transport into certain cells in the body** (striated muscle cells and, to a lesser extent, adipocytes). Glucose uptake in other peripheral tissues, most notably the brain, is insulin-independent.

Insulin Secretion

- **↑ Insulin after a meal:**
 - Stimulates storage of glucose as glycogen
 - Inhibits gluconeogenesis
 - Enhances fat deposition in adipose tissue
 - Increases protein synthesis
- **Fasting state**
 - Counter-regulatory hormones (especially **glucagon**) stimulate glycogen → glucose
- **When glucose unavailable during fasting state**
 - Lipolysis (fat breakdown)
 - Proteolysis (amino acid breakdown)

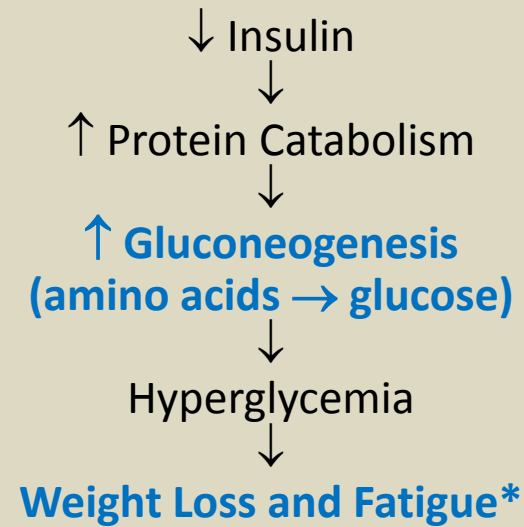


ALTERED CHO METABOLISM

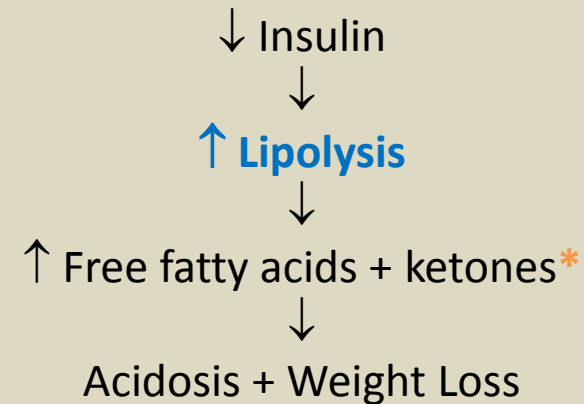


* Hallmark symptoms of diabetes

ALTERED PROTEIN METABOLISM



ALTERED FAT METABOLISM



Diagnostic criteria in diabetes;

Elevation of blood glucose by any one of three criteria:

- A **random blood glucose** concentration of ≥ 200 mg/dL **with classical** signs and symptoms
- A **fasting glucose** concentration ≥ 126 mg/dL **more than one occasion**
- An **abnormal oral glucose tolerance test (OGTT)**, in which the glucose concentration ≥ 200 mg/dL 2 hours after a standard carbohydrate load (75 g of glucose).
- **N.B**
A normal fasting plasma glucose level is currently defined as <100 mg/dL. Patients with fasting glucose levels of 100 to 125 mg/dL are considered to have **"impaired fasting glucose,"** and need to be followed closely because they are at high risk of developing diabetes over time.

Classification of DM

1. Type 1 DM

- It is due to insulin deficiency and is formerly known as.
 - **Type I**
 - **Insulin Dependent DM (IDDM)**
 - **Juvenile onset DM**

2. Type 2 DM

- It is a combined insulin resistance and relative deficiency in insulin secretion and is frequently known as.
 - **Type II**
 - **Noninsulin Dependent DM (NIDDM)**
 - **Adult onset DM**

3. Gestational Diabetes Mellitus (GDM):

- Gestational Diabetes Mellitus (GDM) developing during some cases of pregnancy but usually disappears after pregnancy.

4. Other types:

- Secondary DM

Mechanism of Hyperglycemia in diabetes

- Absolute (type 1 diabetes) or relative (type 2 diabetes):
- An increase in hepatic glucose output
- A decrease in peripheral glucose uptake & utilization.

Type 1 Diabetes Mellitus

- **Formerly known as “juvenile onset” or “insulin dependent” diabetes**
- **Most often occurs in people under 30 years of age**
- **Peak onset between ages 11 and 13**

Type 1 Diabetes Mellitus

Etiology and Pathophysiology

- Progressive **destruction of pancreatic β cells**
- **Autoantibodies** cause a reduction of 80% to 90% of normal β cell function before manifestations occur
- The islets show necrosis of β cell & lymphocytic infiltration (so called **insulitis**)
- **Causes:**
 - Genetic predisposition
 - Exposure to a virus (Coxsackie, Rubella , Mump) triggers autoimmune destruction of β cells

Type 1 Diabetes Mellitus

Onset of Disease

- **Manifestations develop when the pancreas can no longer produce insulin**
 - Rapid onset of symptoms
 - Present at ER with impending or actual ketoacidosis
- **Diabetic ketoacidosis (DKA)**
 - Life-threatening complication of Type 1 DM
 - Occurs in the absence of insulin
 - Results in metabolic acidosis

Type 2 Diabetes Mellitus

- Accounts for **90%** of patients with diabetes
- Usually occurs in people **over 40 years** old
- 80-90% of patients are **overweight**
- Both **genetic & environmental** factors are involved

Type 2 Diabetes Mellitus

Etiology and Pathophysiology

- **Insulin resistance**
 - **Body tissues do not respond to insulin**
 - **Results in hyperglycemia**
- **Decreased (but not absent) production of insulin**
- *Obesity plays an important role in the development of insulin resistance .*

Risk Factors

- **Type 2 DM**

- Family History
- Obesity
- Habitual physical inactivity
- Previously identified impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- Hypertension
- Hyperlipidemia

Type 2 Diabetes Mellitus

Onset of Disease

- **Gradual** onset
- Person may go many years with undetected hyperglycemia
- Marked hyperglycemia

Clinical Presentation

• **Type 1 DM**

- Polyuria
- Polydipsia
- Polyphagia
- Weight loss
- Weakness & fatigue
- Dry skin
- Ketoacidosis

• **Type 2 DM**

- Patients can be asymptomatic
- Polyuria
- Polydipsia
- Polyphagia
- Fatigue
- Weight loss
- Most patients are discovered while performing urine glucose screening

Characteristics	Type 1	Type 2
% of diabetic pop	5-10%	90%
Age of onset	Childhood & Adolescence	Usually > 40 + some obese children
Pathology	β cell depletion, islet atrophy.	Early; inflammation; Late : amyloid deposition in islet. β cell depletion .
Pathogenesis	Autoimmune “ insulitis”	Defect in insulin secretion, tissue resistance to insulin, increased HGO
Family history	Generally not strong	Strong
Obesity	Uncommon	Common
History of ketoacidosis	Often present	Rare except in stress
Clinical presentation	moderate to severe symptoms: 3Ps, fatigue, wt loss and ketoacidosis	Mild symptoms: Polyuria and fatigue. Diagnosed on routine physical examination
Treatment	Insulin, Diet Exercise	Diet ,Exercise Oral antidiabetics,Insulin

Gestational Diabetes

- Develops during **pregnancy**
- Detected at 24 to 28 weeks of gestation
- Associated with ↑ risk for cesarean delivery, perinatal death, and neonatal complications

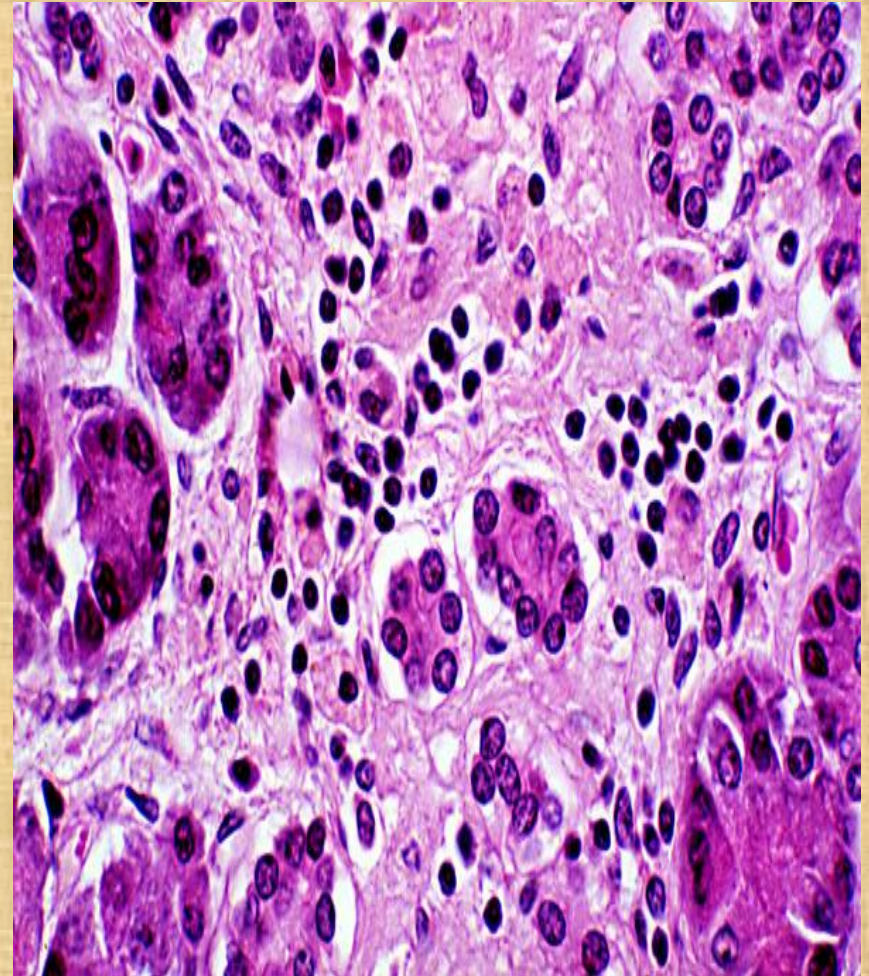
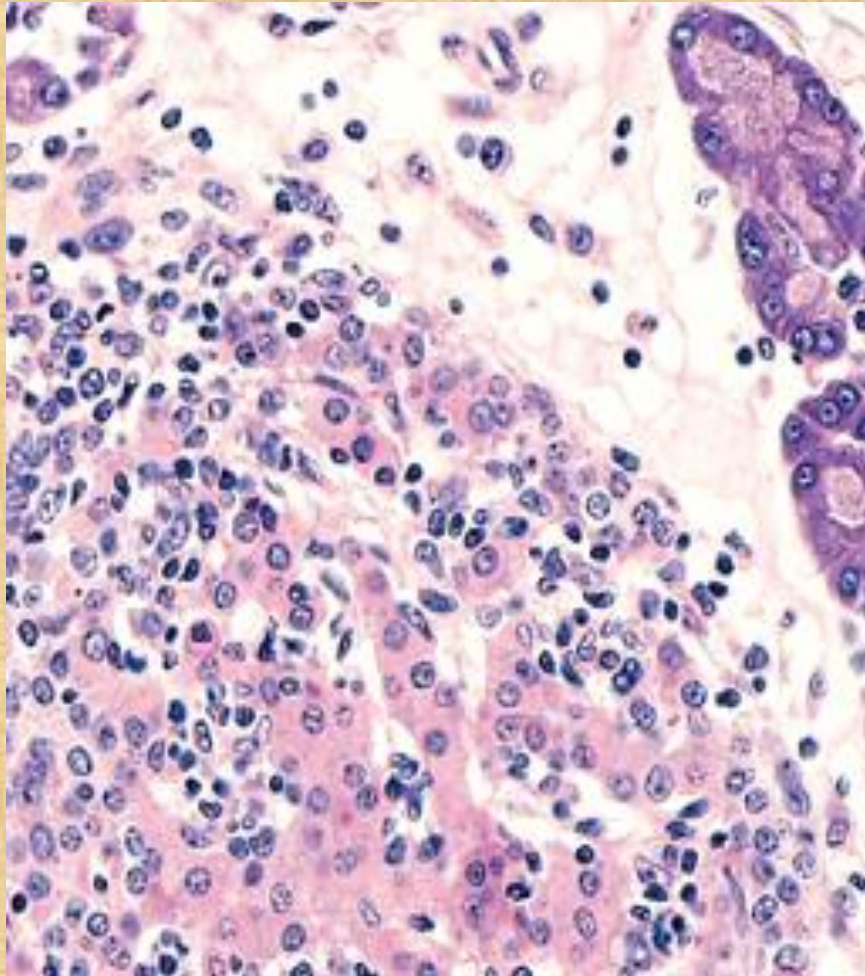
Secondary Diabetes

- Results from another medical condition or due to the treatment of a medical condition that causes abnormal blood glucose levels
 - Cushing syndrome (e.g. steroid administration)
 - Hyperthyroidism
 - Parenteral nutrition

Lesions in the pancreas

- **Reduction in the number and size of islets** ; mostly seen in type 1 diabetes, particularly with rapidly advancing disease.
- **Leukocytic infiltration of the islets**, which are principally composed of mononuclear cells (lymphocytes and macrophages). Seen in both type 1 & early stage of type 2 .
- **Amyloid replacement of islets in long-standing type 2 diabetes**, deposition of pink, amorphous material beginning in and around capillaries and between cells. Islets may be obliterated & fibrosis may be observed.

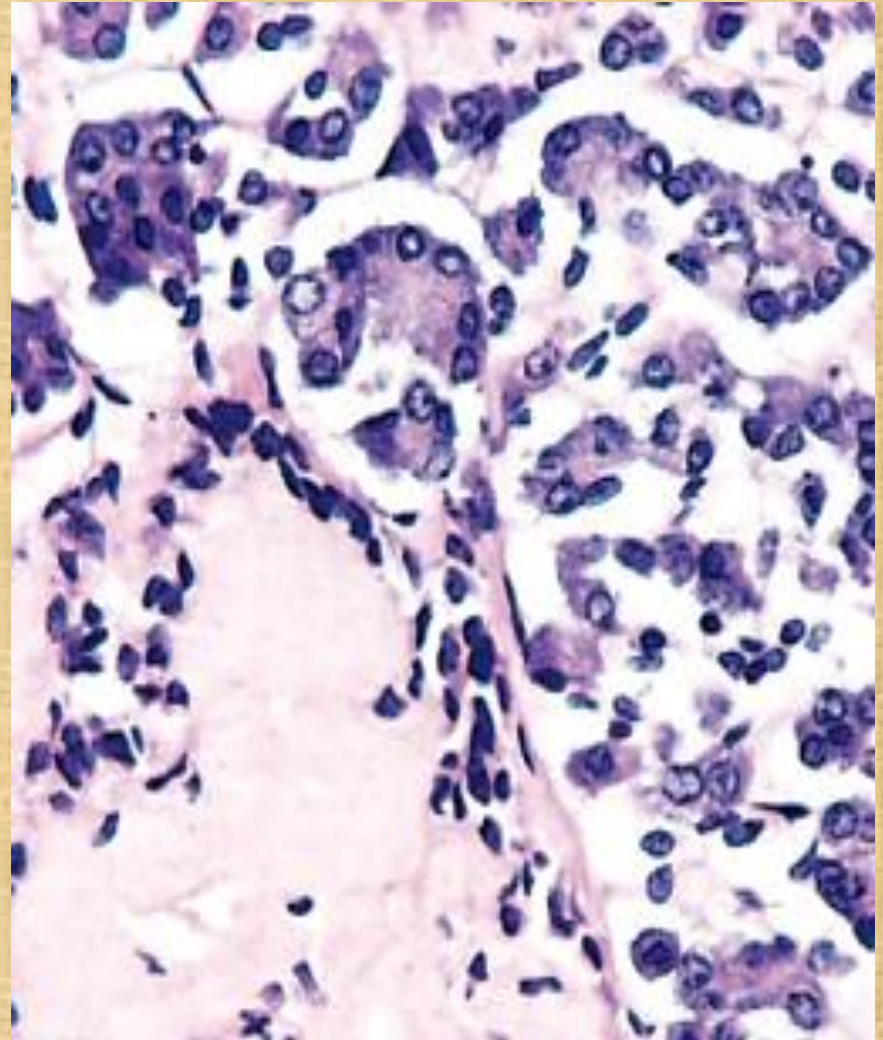
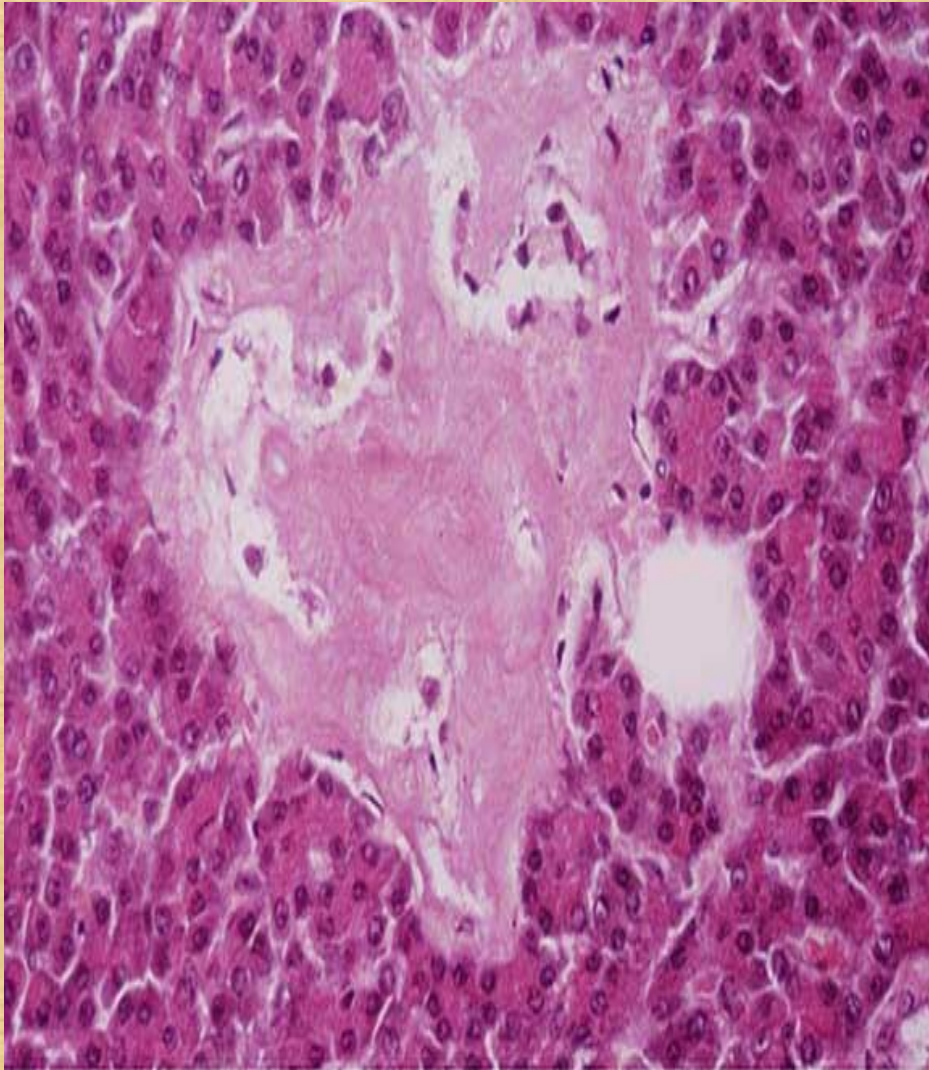
Autoimmune insulitis in type 1 human diabetes.



Type II DM , Pathology

- No consistent reduction in the number of B-cells
- No morphologic lesions of B- cells
- In some islets, fibrous tissue accumulates, sometimes to such a degree that they are obliterated.
- Islet amyloid is often present particularly in patients over 60 years of age.

Amyloidosis of a pancreatic islet in type 2 diabetes.



Acute Complication in D.M. ;

1- Hypoglycemia

2- DKA

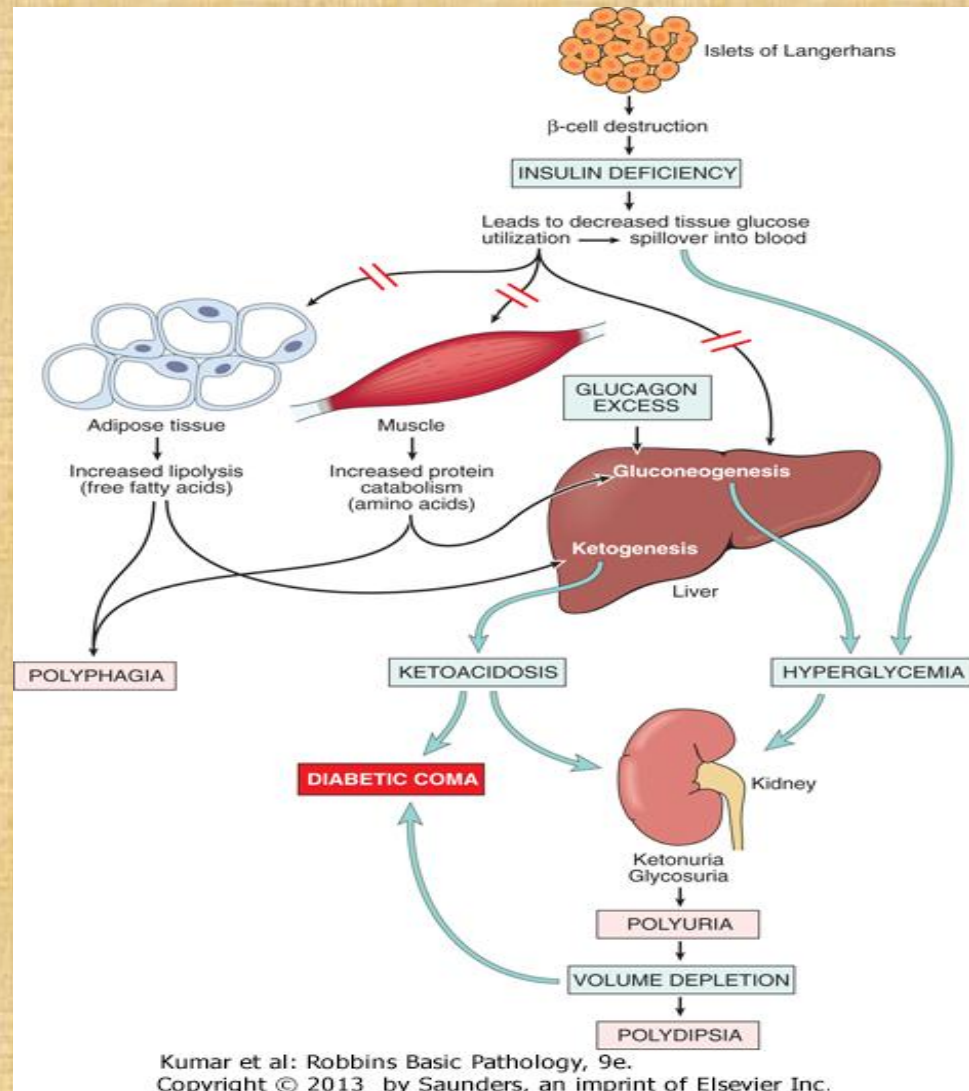
• Pathophysiology

– Continuation of effects of insulin deficiency

- Severe metabolic acidosis
- Severe dehydration → shock
- Severe electrolyte imbalance

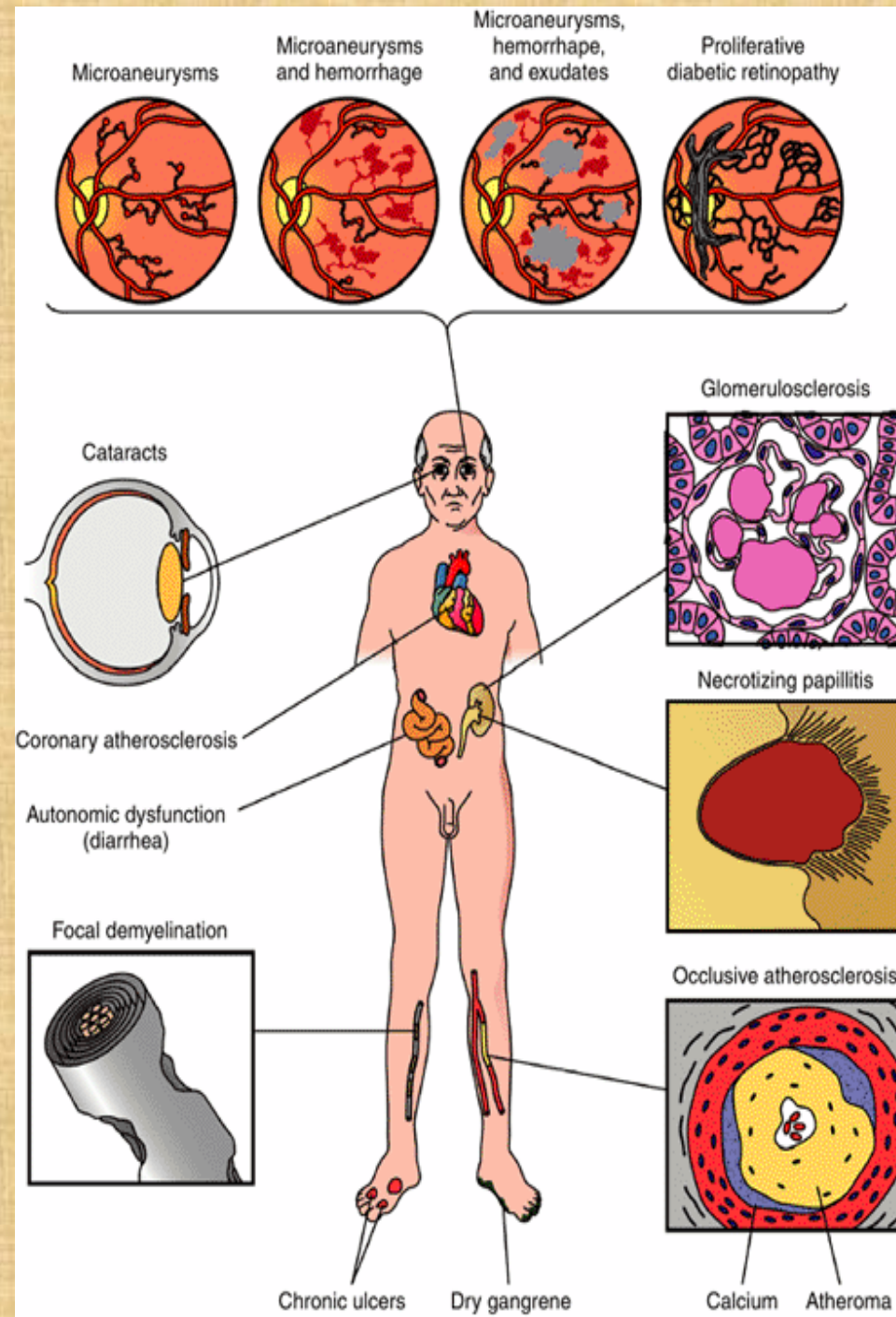
• Clinical Manifestations

- S/S dehydration (↑ HR; ↓ BP, dry MM),
- Fruity breath (acetone)
- Abdominal pain



Chronic Complications in D.M.;

- **Angiopathy – blood vessel disease (Hyaline arteriolosclerosis) .**
- **amorphous, hyaline thickening of the wall of the arterioles, which causes narrowing of the lumen.**
- **(Diabetic macrovascular disease),** basement membranes of small vessels.
- **(Diabetic microangiopathy),** thickening is evident in the capillary of kidneys (**diabetic nephropathy**), retina (**retinopathy**), nerves (**neuropathy**), and other tissues.



D.M ; Chronic Complications

➤ Microvascular

➤ Retinopathy (Diabetic retinopathy)

- Leading cause of new blindness
- Vessel occlusion → aneurysms → leakage of fluid
- Vessel occlusion → new vessel growth → hemorrhage, exudate, neovascularization, retinal detachment & blindness

➤ Nephropathy (Diabetic nephropathy)

- Damage to vessels supplying glomeruli
- Leading cause of ESRD

➤ Neuropathy (Diabetic neuropathy)

➤ Sensory Neuropathy

- Loss of sensation, abnormal sensation, pain of hands and/or feet
- Can progress to partial or complete loss of sensitivity to touch and temperature → high risk of injury without pain
- Rx is glucose control

➤ Autonomic neuropathy. Examples:

- Hypoglycemic unawareness
- Silent MI
- Erectile dysfunction, decreased libido
- Neurogenic bladder → urine retention

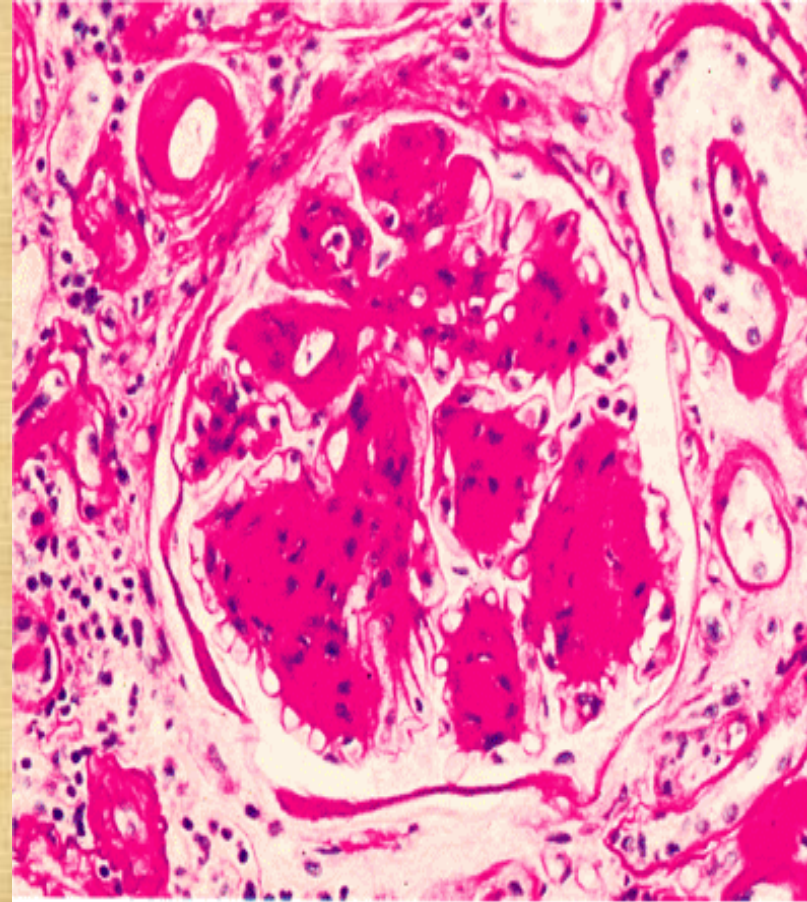


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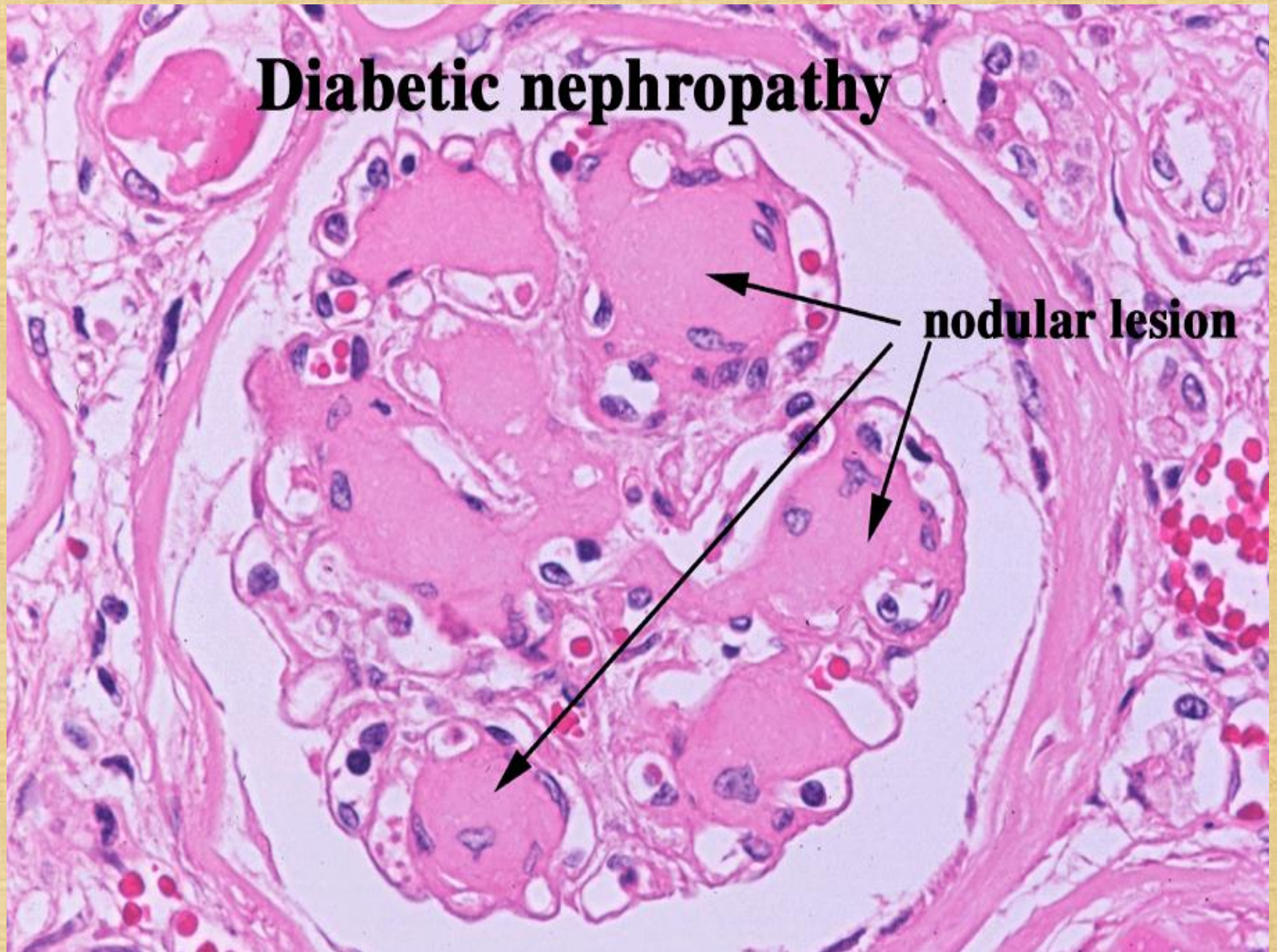
Diabetic Nephropathy

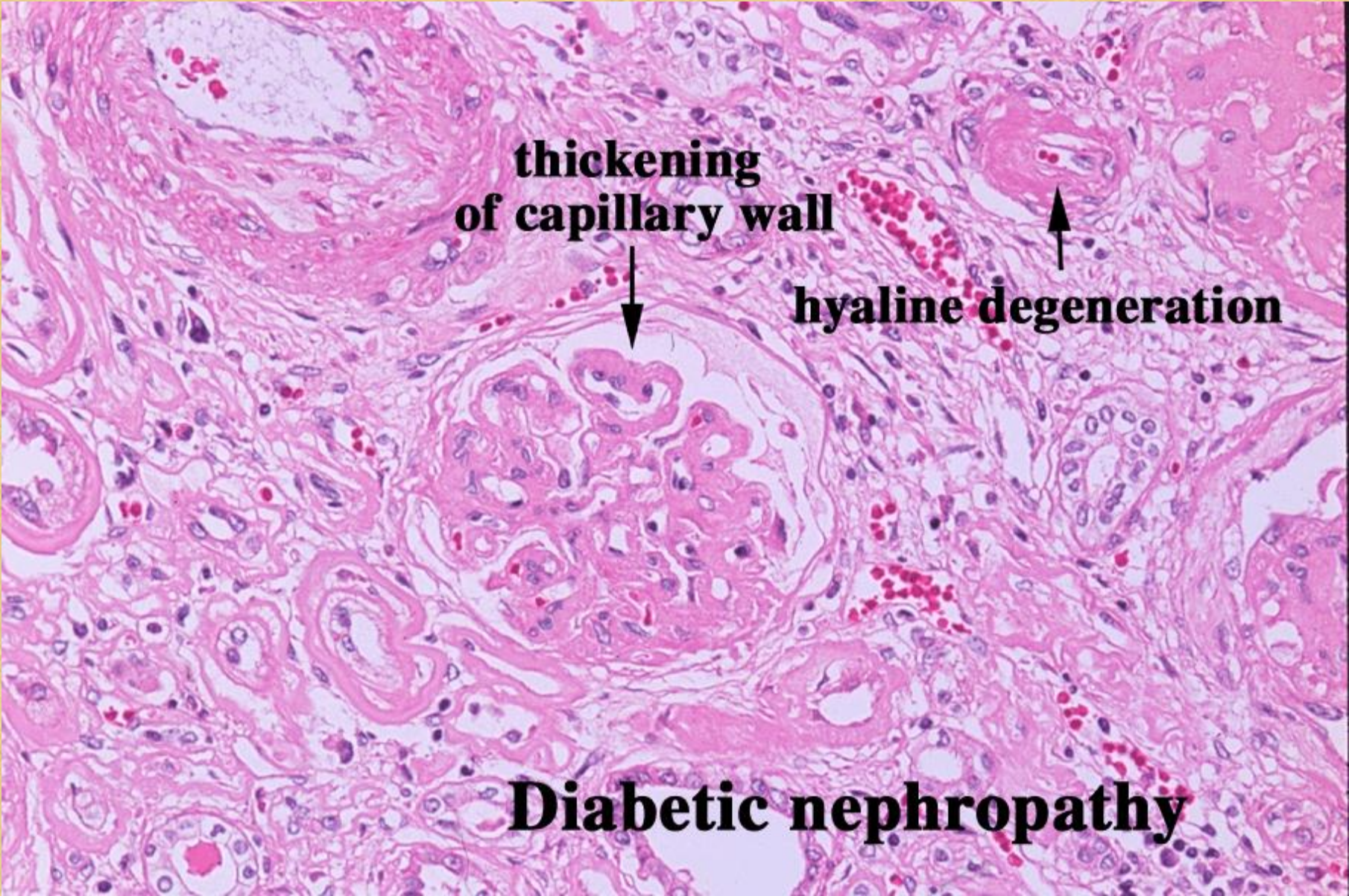
Three lesions :

- (1) glomerular lesions; capillary basement membrane thickening; diffuse mesangial sclerosis and nodular glomerulosclerosis “**Kimmelstiel-Wilson disease**”
 - despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins (**Microalbuminurea**).
 - (2) renal vascular **arteriolosclerosis**;
 - (3) pyelonephritis, including **necrotizing papillitis**.
- **Diabetic nephropathy accounts for one third of all new cases of renal failure.**



Diabetic nephropathy



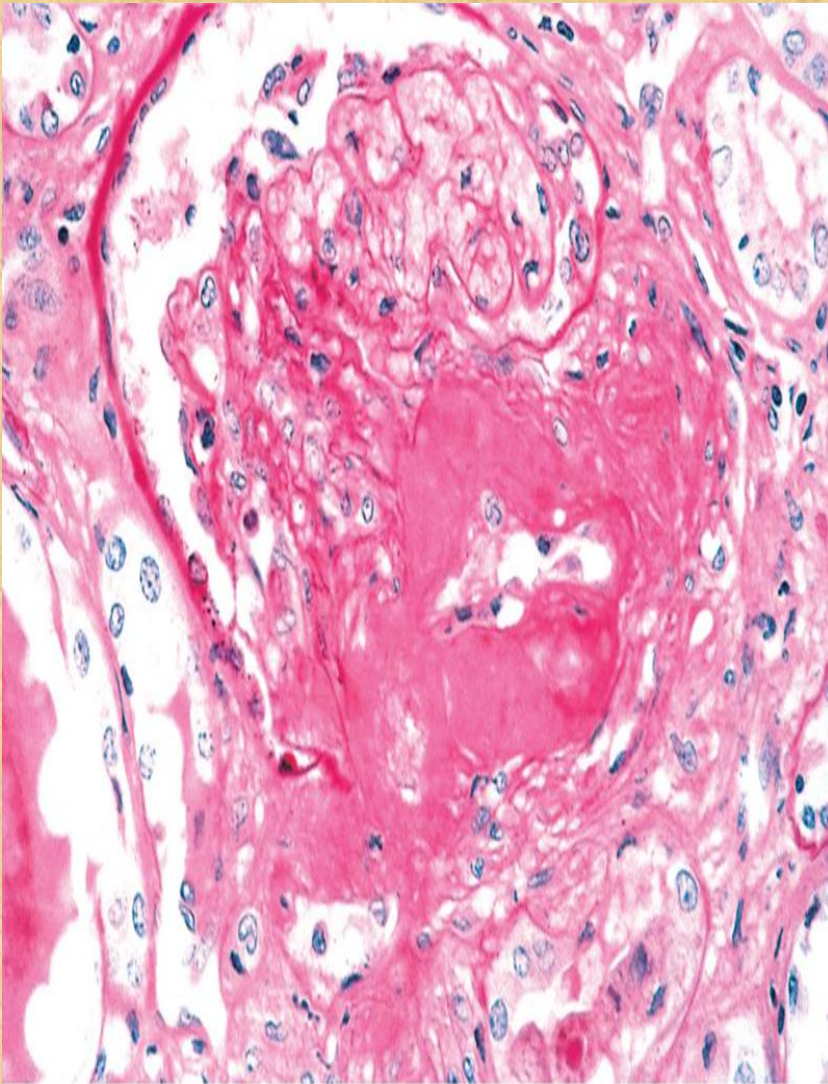


A histological slide of a kidney section stained with hematoxylin and eosin (H&E). The image shows several glomeruli. One glomerulus in the center is highlighted with a black arrow pointing to its thickened capillary wall. Another black arrow points to a cluster of red blood cells in a nearby capillary, labeled as hyaline degeneration. The surrounding tissue shows various cellular structures and some interstitial changes.

**thickening
of capillary wall**

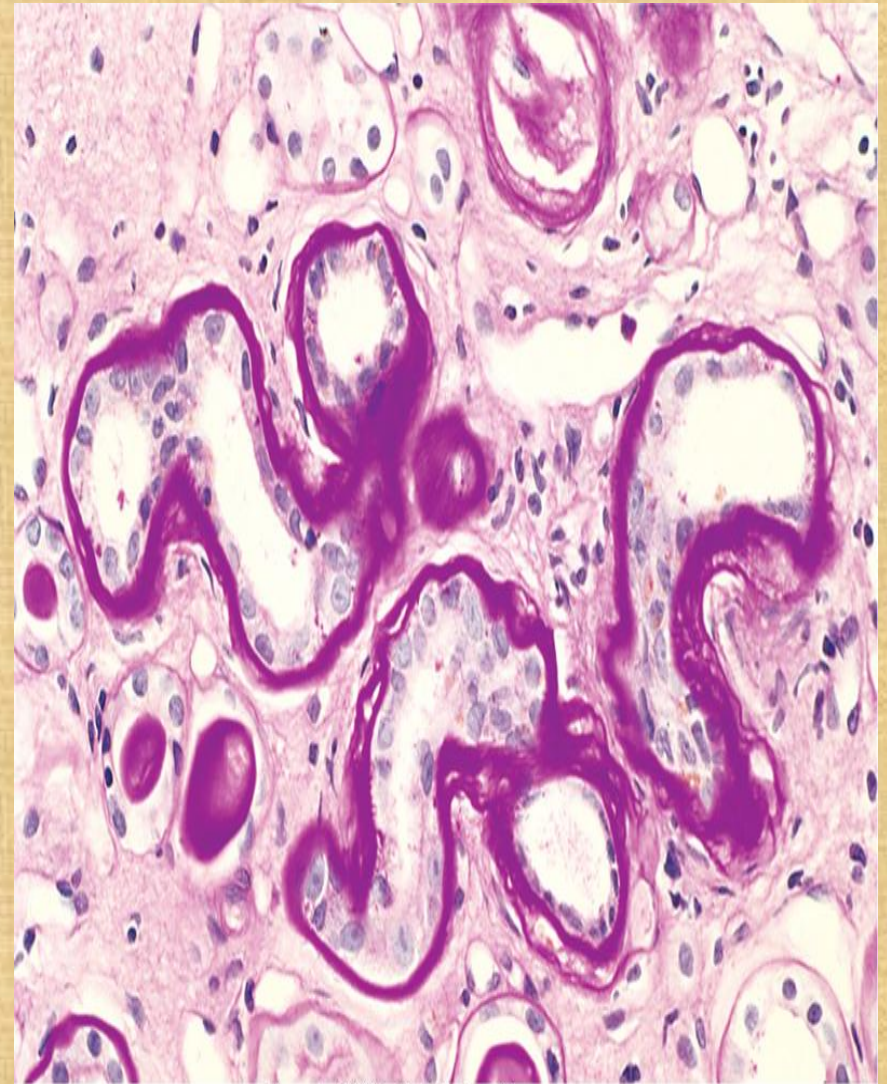
hyaline degeneration

Diabetic nephropathy



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- **Severe renal hyaline arteriosclerosis, markedly thickened, tortuous vascular wall arteriole .**



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- **Renal cortex showing thickening of tubular basement membranes**



- **Nephrosclerosis**; the kidney shows **diffuse granular** transformation of the surface (*left*) & marked **thinning of the cortical tissue** (*right*), some **irregular depressions**, the result of **pyelonephritis**, and an incidental **cortical cyst** (*far right*).

Diabetic Neuropathy

- The **most common** complications of diabetes.
- Characterized by **pain and abnormal sensations** in the extremities.
- Affects **Sensory and Autonomic** Innervations, **Peripheral sensory impairment**, and autonomic nerve dysfunction.
- Due to **microvasculopathy** involving the small blood vessels of nerves .

Diabetes Mellitus

Chronic Complications

- **Infection**
 - **Bacterial and Fungal Infections Occur in Diabetic Hyperglycemia is Poorly Controlled**
 - Immune deficiencies
 - Delayed detection d/t sensory neuropathy
 - Decreased circulation – delays or prevents immune response

Diabetes Mellitus

Chronic Complications

- **Diabetic Foot**

- **Macrovascular** disease → PVD (↓ supply of oxygen, WBCs, nutrients)
- **Sensory neuropathy** → injury



Diabetes Mellitus

Diagnostic Studies

- **Glucosuria**
- **Ketonuria**
- **Fasting plasma glucose level ≥ 120 mg/dL**
- **Random plasma glucose level ≥ 200 mg/dL plus symptoms**
- **Impaired Glucose Tolerance Test – patient is “challenged” with glucose load. Patient should be able to maintain normal BG. Diabetes if BG > 200 mg/dL 2 hr post challenge**
- **Hemoglobin A1C test (glycosylated Hgb)**
 - **Reflects amount of glucose attached to Hgb over life of RBC**
 - **Indicates overall glucose control over previous 90 – 120 days**

Treatment

General approaches

- Medications
- Dietary and exercise modification
- Regular complication monitoring
- Self monitoring of blood glucose
- Control of BP and lipid level